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Changes in the Energy Substrate after Hepatectomy —Preferential Utilization of Fatty Acids and its Effect on Hepatic Regeneration after Major Hepatectomy—

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Summary

Changes in the energy substrate utilized by the remnant liver after hepatectomy were studied in relation to the hepatic energy status in 25, 70, and 93% hepatectomized rabbits. In 25% hepatectomized rabbits, the energy charge $((ATP + 0.5ADP)/(ATP + ADP + AMP))$ level of the remnant liver remained unchanged after hepatectomy, and was not affected by portal infusion of (+)-octanoylcarnitine, an inhibitor of fatty acid oxidation. The energy substrate utilized in the remnant liver after 25% hepatectomy was predominantly glucose, rather than fatty acids. In contrast, the energy charge level of the remnant liver decreased rapidly after 70% hepatectomy and reached the lowest level of 0.77 at 12–24 hours after hepatectomy ($p < 0.01$). At this time, the energy charge level was further decreased to 0.51 by (+)-octanoylcarnitine ($p < 0.001$). Afterward, it returned to near normal level at 96 hours after hepatectomy. At this time, the effect of (+)-octanoylcarnitine was less evident, with the restoration of the energy charge. On the other hand, portal infusion of sodium fluoride, an inhibitor of glycolysis, decreased the energy charge level at 96 hours, rather than at 12 and 24 hours after 70% hepatectomy. In 93% hepatectomized rabbits, the energy charge level of the remnant liver decreased rapidly and steeply in the phase immediately following hepatectomy. It is suggested that the remnant liver metabolism switches to predominant utilization of fatty acid as an energy source when the energy charge decreases; it then becomes able to utilize glucose with the restoration of energy charge level.

Key Words: Partial hepatectomy, Fatty acid oxidation, Energy substrate, (+)-Octanoylcarnitine, Hepatic regeneration

索引用語: 肝切除, 脂肪酸化, エネルギー基質, (+)-オクタノイルカルチン, 肝再生.

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Introduction

Postoperative hypoglycemia during the immediate phase following major hepatic resection has been recognized as a serious problem, and the infusion of a hyperosmolar glucose solution has been generally recommended for this period^{18,19,31,38}. However, recent studies in our laboratory show evidence of a marked glucose intolerance in the early critical period after massive hepatic resection^{11,33}. Although it is necessary to maintain blood sugar level to prevent damage to the brain and other tissues, the question arose whether glucose, if offered in excess during the early stages of the regenerating processes, is in fact being utilized as a substrate in the energy metabolism of the remnant liver after major hepatic resection. The major processes in the supply and consumption of energy in cells are mainly dependent on the oxidation of carbohydrate or fatty acids. In this study, (+)-octanoylcarnitine²¹, a potent inhibitor of fatty acid oxidation^{22,48}, and sodium fluoride⁴⁰, an inhibitor of glycolysis, were administered to partially hepatectomized rabbits in order to clarify the energy sources utilized by the remnant liver, particularly in relation to the resected hepatic mass and the hepatic energy status^{24,25}. Moreover, the effect of fatty acid oxidation on the rate of DNA synthesis in the regenerating liver was examined²⁷. Evidence will be presented indicating that the metabolism of the remnant liver switches to fatty acid utilization as the predominant energy source concomitantly with a decrease in the energy charge¹; it then reverts to a greater utilization of glucose in the course of the restoration of the energy charge level with a lessened ability to oxidize fatty acid. In addition, the inadvisability of hyperosmolar glucose administration during the phase immediately following massive hepatic resection will be discussed.

Methods

Healthy young male rabbits, weighing between 1.8 and 2.3 kg, were maintained on a diet of Clea CR-2 (Nippon Haigoshiryo Co. Ltd., Osaka, Japan) and water ad libitum preoperatively for about two weeks, and then fasted for 15 hours before operation. The rabbits were anesthetized by intravenous injection of 15 mg per kg body weight of sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate.

In 25% hepatectomized rabbits, the right posterior lobe was resected. In 70% hepatectomized rabbits, the left anterior, right anterior and right posterior lobes were resected. In 93% hepatectomized rabbits, the right anterior, right posterior, left anterior and left posterior lobes were resected, leaving only the central lobe intact. In sham-operated rabbits, laparotomy and mobilization of the liver were carried out. Normal control rabbits were fed, not operated on.

In those rabbits that received portal infusion of (+)-octanoylcarnitine or sodium fluoride, a catheter was inserted into the portal vein at the beginning of the portal infusion. In 70% hepatectomized rabbits, a total amount of 5 μ moles of (+)-octanoylcarnitine or 200 μ moles of sodium fluoride, which had been dissolved in 20 ml saline and neutralized to pH 7.4 with NaOH, was intraportally infused by an infusion pump via the catheter for 3 hours beginning at 12, 24, 48, or 96 hours after hepatectomy. In 25% hepatectomized rabbits, (+)-octanoylcarnitine

infusion was maintained for 3 hours beginning at 12 hours after the operation. In control subjects, saline was infused instead of (+)-octanoylcarnitine or sodium fluoride solution. The rabbits that received portal infusion at 12 hours after the operation were fasted postoperatively. Other rabbits that received portal infusion at 24, 48, or 96 hours after the operation were fed postoperatively but were fasted again for 15 hours before infusion.

In those rabbits that received intravenous feeding postoperatively, a 20% glucose solution was administered at the rate of 2 ml/kg body weight/hour through a catheter inserted into the marginal ear vein.

For assays of ketone bodies, non-esterified fatty acid (NEFA), and blood sugar, the arterial blood samples were obtained at the beginning and end of portal infusion from a catheter inserted into the femoral artery.

To measure acetoacetate and β -hydroxybutyrate, 3 ml of arterial blood sample was mixed with 6 ml of ice-cold 6% (w/v) perchloric acid solution immediately after the blood sample was taken, and centrifuged at $10,000 \times g$ for 5 minutes at $0-4^{\circ}\text{C}$. The supernatant was adjusted to pH 5.5–6.0 with cold 69% (w/v) K_2CO_3 and recentrifuged at $10,000 \times g$ for 5 minutes at $0-4^{\circ}\text{C}$. The supernatant was used to determine the ketone body concentrations. Acetoacetate and β -hydroxybutyrate were measured using enzymatic methods^(23,47). Blood sugar level was determined by the *o*-toluidine methods⁽¹⁰⁾. Serum NEFA level was measured by the method of LAURELL et al.⁽¹⁶⁾.

For the assay of hepatic adenine nucleotides, liver tissue obtained at the end of the portal infusion was clamped and frozen in situ with stainless steel tongs pre-cooled in liquid nitrogen. The frozen tissue was removed and immersed in liquid nitrogen through which (O) had been bubbled. The entire procedure was completed within 10 seconds. The frozen tissue was then powdered by stainless-steel mortar and pestle in a liquid nitrogen bath. The powdered tissue was weighed and added to three volumes of 5% ice-cold perchloric acid including 1 mM-EDTA solution. The powdered tissue was then homogenized in a glass homogenizer with a motor-driven pestle and centrifuged at $10,000 \times g$ for 15 minutes at $0-4^{\circ}\text{C}$. The supernatant was adjusted to pH 5.5–6.0 with cold 69% (w/v) K_2CO_3 and recentrifuged at $10,000 \times g$ for 5 minutes at $0-4^{\circ}\text{C}$. The supernatant was used for analysing adenine nucleotides. ATP was determined enzymatically with hexokinase and glucose-6-phosphate dehydrogenase by the standard spectrophotometric method, reading the absorbance of NADH at 340 nm ⁽¹⁵⁾. ADP and AMP were determined similarly with lactate dehydrogenase, pyruvate kinase, and myokinase⁽¹²⁾. The energy charge level, which indicates the intracellular energy status, was calculated as follows:⁽¹⁾

$$\text{energy charge} = (\text{ATP} + 0.5\text{ADP}) / (\text{ATP} + \text{ADP} + \text{AMP})$$

Hepatic adenine nucleotides and the energy charge level were determined on whole liver tissue samples.

Mitochondria were prepared by methods previously reported elsewhere⁽³⁴⁾. Oxygen consumption was measured polarographically with a rotating electrode, at 22°C at pH 7.4 in a medium containing 0.3 M mannitol, 0.01 M KCl, 0.04 M MgCl_2 , 0.01 M Tris HCl buffer, 0.005 M potassium phosphate buffer, 0.2 mM EDTA, and $230 \mu\text{M}$ ADP. Glutamate was

added at a concentration of 0.4 mM as a substrate³⁵⁾. Mitochondrial phosphorylative activity, which indicates the mitochondrial ATP-synthesizing ability, was calculated as follows:

$$\text{Mitochondrial phosphorylative activity} = \text{state 3 respiration} \times \text{ADP/O}$$

Where, state 3 respiration is being expressed as $\text{m}\mu$ atoms of oxygen consumed per minute per milligram of mitochondrial protein in the presence of ADP and succinate, and ADP/O ratio being calculated as the quotient of added ADP to the amount of oxygen utilized in state 3 respiration. Therefore, the phosphorylative activity was expressed as nanomoles ATP synthesized per minute per milligram of mitochondrial protein. Mitochondrial protein was determined by the method of LOWRY et al.¹⁷⁾ with crystalline serum albumin as a standard.

To study the effects of (+)-octanoylcarnitine on DNA synthesis, 100 $\mu\text{Ci/kg}$ of methyl-³H-thymidine (specific radioactivity 46 Ci/mmol) was injected intravenously one hour after the beginning of intraportal infusion of (+)-octanoylcarnitine. Liver tissue was obtained 2 hours after the injection of the radioisotope. Portal infusion was thus continued for 3 hours in all, during which time a total amount of 5 μmol of (+)-octanoylcarnitine was infused. The extraction of DNA was performed as described by SCHNEIDER³⁹⁾, and 10 ml of scintillant (0.4% 2,5-diphenyloxazol and 0.02% 1,4-bis-2-(5-phenyloxazolyl)-benzene in dioxan) was added to 1 ml of DNA extract. Tritium radioactivity was counted in a liquid scintillation spectrometer (Isocap 300/Nuclear Chicago) with correction for quenching by the channel ratios method. DNA in the assay extract was determined by a modification of the diphenylamine reaction described by BURTON⁴⁾, in which sulfuric acid was omitted and the diphenylamine content was increased to 2 g/100 ml, giving a final concentration of perchloric acid of 0.5 mol/l¹⁴⁾. Highly polymerized calf thymus DNA was used as a standard. All samples for determining the rate of DNA synthesis were analysed in duplicate.

Results are expressed as means \pm standard errors. All statistical analyses were based on Student's t-test.

Results

Time courses of changes in energy charge and mitochondrial phosphorylative activity of the remnant liver following resection in 25, 70, and 93% hepatectomized rabbits are shown in Fig. 1.

In 25% hepatectomized rabbits, the energy charge level of the remnant liver did not decrease significantly after the operation, nor did the mitochondrial phosphorylative activity increase significantly.

In 70% hepatectomized rabbits, the energy charge level of the remnant liver decreased rapidly and reached the lowest level of 0.773 at 24 hours after hepatectomy ($p < 0.01$). It then returned to the preoperative level within 7 days after the operation. In contrast, mitochondrial phosphorylative activity increased rapidly and reached 170% of the control level at 24 hours after 70% hepatectomy ($p < 0.01$). It also returned to the preoperative level within 7 days after the operation.

In 93% hepatectomized rabbits, the energy charge level of the remnant liver showed a rapid

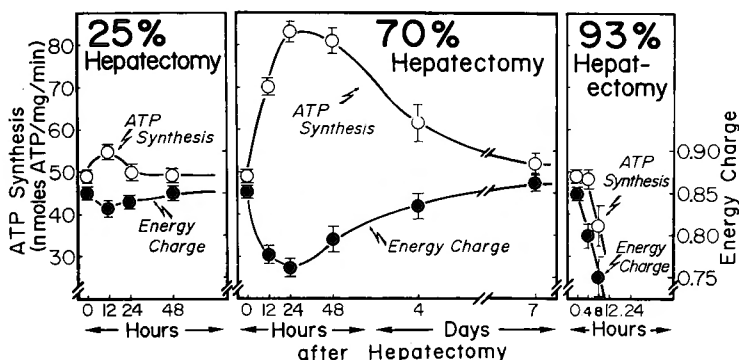


Fig. 1. Changes in energy charge level and mitochondrial phosphorylative activity following 25, 70, and 93% hepatectomy of rabbits. Each point represents the mean and standard error of values for five or more animals.

and steep decrease in the phase immediately following hepatectomy. The compensatory enhancement of mitochondrial phosphorylative activity could not occur in this extensive major hepatic resection. The phosphorylative activity of the remnant liver continued to decrease, and, thus the energy charge level of the remnant liver also decreased markedly. Consequently, all rabbits in this group died within 12 hours after the operation.

Changes in blood ketone body ratio (acetoacetate/ β -hydroxybutyrate) in 25, 70 and 93% hepatectomized rabbits after the operation are shown in Fig. 2. In 25% hepatectomized rabbits, blood ketone body ratio decreased slightly, but returned to a normal level at 48 hours after hepatectomy. In 70% hepatectomized rabbits, blood ketone body ratio rapidly decreased to 0.415 at 12 hours, but it returned to a near normal level at 96 hours after hepatectomy. In 93% hepatectomized rabbits, blood ketone body ratio decreased drastically in the phase immediately after the operation. All rabbits that underwent 93% hepatectomy died within 12 hours after the operation.

The effects of portal infusion of (+)-octanoylcarnitine on hepatic adenine nucleotides after 70% hepatectomy are shown in Table 1, and the time courses of effects of the portal infusion of (+)-octanoylcarnitine and those of sodium fluoride on the energy charge levels of the remnant liver after 70% hepatectomy are shown in Fig. 3. In normal rabbits, energy charge level and

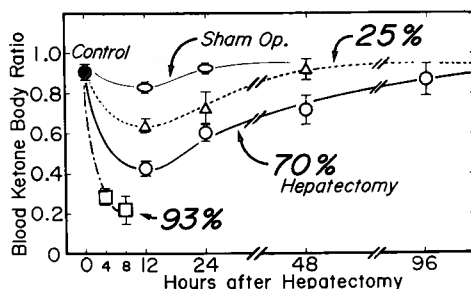


Fig. 2. Changes in blood ketone body ratio (acetoacetate/ β -hydroxybutyrate) following resection in 25, 70, and 93% hepatectomized rabbits. Each point represents the mean and standard error of values for four or more animals.

Table 1. Effects of portal infusion of (+)-octanoylcarnitine on hepatic adenine nucleotides after 70% hepatectomy.

Stage & Treatment	(n)	Adenine Nucleotides (μ moles/gr wet liver)				Energy Charge
		ATP	ADP	AMP	Total	
Normal Control	(11)	2.88 \pm 0.10	0.55 \pm 0.03	0.13 \pm 0.01	3.57 \pm 0.10	0.885 \pm 0.006
+ Saline Inf.	(4)	2.58 \pm 0.05	0.83 \pm 0.11	0.21 \pm 0.04	3.61 \pm 0.19	0.829 \pm 0.022
+ O.C. Inf.	(5)	2.55 \pm 0.11	0.78 \pm 0.11	0.20 \pm 0.03	3.54 \pm 0.29	0.833 \pm 0.010
12 hours after						
Sham Operation	(4)	2.06 \pm 0.04	0.60 \pm 0.06	0.15 \pm 0.09	2.81 \pm 0.10	0.840 \pm 0.014
Hepatectomy	(4)	1.75 \pm 0.07	0.78 \pm 0.09	0.20 \pm 0.03	2.73 \pm 0.16	0.782 \pm 0.015
+ Saline Inf.	(5)	1.46 \pm 0.02	0.83 \pm 0.08	0.35 \pm 0.04	2.64 \pm 0.10	0.701 \pm 0.010
+ O.C. Inf.	(7)	0.81 \pm 0.10 ^a	1.01 \pm 0.05	0.77 \pm 0.13 ^c	2.59 \pm 0.10	0.510 \pm 0.039 ^b
24 hours after						
Sham Operation	(7)	2.32 \pm 0.06	0.54 \pm 0.04	0.16 \pm 0.06	3.02 \pm 0.09	0.860 \pm 0.007
Hepatectomy	(7)	1.74 \pm 0.06	0.84 \pm 0.03	0.21 \pm 0.01	2.79 \pm 0.05	0.773 \pm 0.008
+ Saline Inf.	(6)	1.42 \pm 0.12	0.81 \pm 0.12	0.34 \pm 0.06	2.56 \pm 0.14	0.706 \pm 0.025
+ O.C. Inf.	(4)	0.87 \pm 0.06 ^e	0.75 \pm 0.11	0.53 \pm 0.01 ^e	2.14 \pm 0.27	0.579 \pm 0.006 ^e
48 hours after						
Hepatectomy	(4)	2.14 \pm 0.06	0.79 \pm 0.05	0.27 \pm 0.01	3.20 \pm 0.12	0.793 \pm 0.001
+ Saline Inf.	(4)	1.91 \pm 0.33	1.17 \pm 0.12	0.30 \pm 0.05	3.36 \pm 0.37	0.738 \pm 0.034
+ O.C. Inf.	(5)	1.62 \pm 0.30	1.10 \pm 0.19	0.39 \pm 0.08	3.11 \pm 0.45	0.689 \pm 0.062
96 hours after						
Hepatectomy	(6)	2.25 \pm 0.08	0.76 \pm 0.05	0.22 \pm 0.03	3.23 \pm 0.22	0.819 \pm 0.013
+ Saline Inf.	(4)	1.82 \pm 0.11	0.97 \pm 0.12	0.23 \pm 0.05	3.01 \pm 0.19	0.763 \pm 0.075
+ O.C. Inf.	(6)	1.87 \pm 0.18	0.91 \pm 0.10	0.31 \pm 0.04	3.09 \pm 0.17	0.745 \pm 0.033

Values given are means \pm SEM. Numbers in parentheses indicate number of animals. Total=total adenine nucleotides. Inf.=infusion. O.C.=(+)-octanoylcarnitine.

a= $p<0.001$, b= $p<0.01$, c= $p<0.05$ compared with saline infused group of the same stage.

adenine nucleotides levels were not affected by the (+)-octanoylcarnitine infusion, when compared with those for saline infusion. In contrast, at 12 hours after 70% hepatectomy, energy charge level decreased dramatically to 0.510 ($p<0.001$) after the infusion of (+)-octanoylcarnitine compared with 0.701 in saline infused rabbits, concomitantly with a decrease in ATP and an increase in AMP. At 24 hours after 70% hepatectomy, the infusion of (+)-octanoylcarnitine decreased the energy charge level to 0.579, compared with 0.706 in saline infused rabbits ($p<0.01$). The differences in adenine nucleotides levels and energy charge levels between (+)-octanoylcarnitine infused rabbits and saline infused rabbits were less evident at 48 and 96 hours. On the contrary, sodium fluoride decreased the energy charge level at 96 hours, rather than at 12 and 24 hours, although the decreases were all statistically insignificant.

Fig. 4 shows the time courses of NEFA level, total ketone body concentrations (acetoacetate+ β -hydroxybutyrate) and ketone body ratio (acetoacetate/ β -hydroxybutyrate) in the arterial blood of 70% hepatectomized rabbits. NEFA level increased rapidly after 70% hepatectomy and reached 0.98 mEq/L at 12 hours after the operation. It then rapidly returned to a near normal level of 0.59 mEq/L at 48 hours after 70% hepatectomy. Total ketone body concentrations in

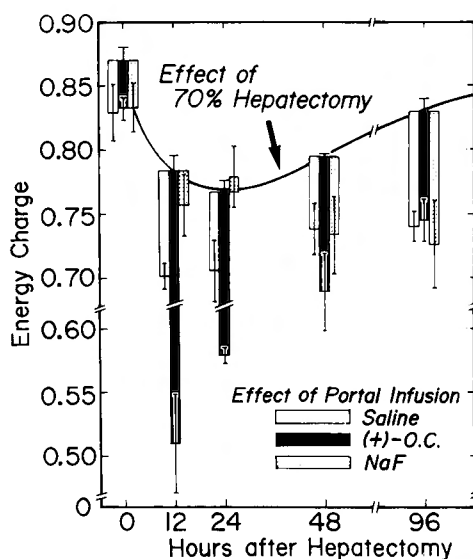


Fig. 3. Time course of changes in energy charge level after 70% hepatectomy of rabbits, and the effects of portal infusion of (+)-octanoylcarnitine and sodium fluoride on the energy charge level in these rabbits. Curved line shows the changes in energy charge after 70% hepatectomy. Vertical bars starting from the curved line indicate the effects of portal infusion on the energy charge level of the remnant liver. Each point and end of bar represents the mean, and small vertical lines indicate the standard errors of values for four or more animals.

the blood also increased concomitantly with the increase in NEFA level, and reached 300% of the normal level at 24 hours, before returning to near normal levels at 96 hours.

The effects of portal infusion of (+)-octanoylcarnitine and sodium fluoride on total ketone

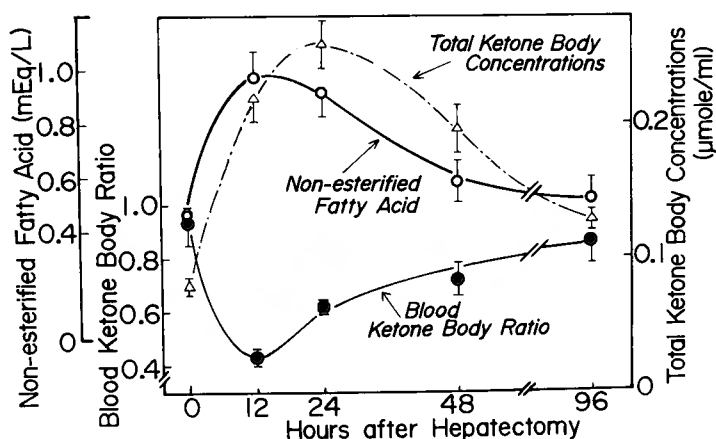


Fig. 4. Time course of changes in non-esterified fatty acid level, total ketone body concentrations (acetoacetate + β -hydroxybutyrate) and ketone body ratio (acetoacetate/ β -hydroxybutyrate) in arterial blood after 70% hepatectomy of rabbits. Each point represents the mean and standard error of values for seven or more animals.

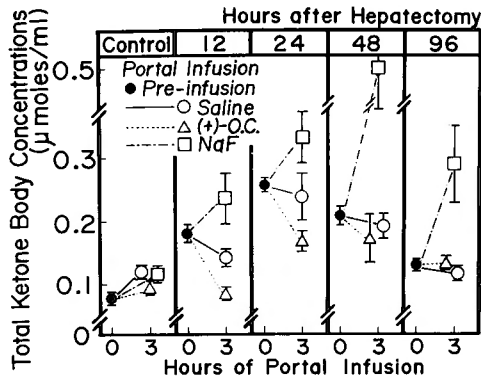


Fig. 5. Effects of portal infusion of (+)-octanoylcarnitine and sodium fluoride on total ketone body concentrations in the blood after 70% hepatectomy. Each point represents the mean and standard error of values for four or more animals.

body concentrations in the blood after 70% hepatectomy are shown in Fig. 5. In normal rabbits, total ketone body concentrations in the blood were not affected by (+)-octanoylcarnitine infusion. At 12 hours after 70% hepatectomy, total ketone body concentrations in the blood were higher than those in normal rabbits, indicating an enhancement in β -oxidation. However, the concentrations of total ketone body decreased significantly following 3 hours of (+)-octanoylcarnitine infusion ($0.01 < p < 0.05$). At 24 hours after the operation, (+)-octanoylcarnitine infusion also decreased total ketone body concentrations in the blood significantly ($p = 0.05$). But at 48 and 96 hours after the operation, total ketone body concentrations were not affected by (+)-octanoylcarnitine infusion. In contrast, the infusion of sodium fluoride increased the total ketone body concentrations in the blood highly and significantly at 48–96 hours after hepatectomy.

Table 2 shows NEFA, ketone body ratio and total ketone body concentrations in arterial blood at 12 hours after 25 and 70% hepatectomy. NEFA level did not increase after 25% hepatectomy. Although ketone body ratio in arterial blood decreased and reached the lowest level at 12 hours after 25% hepatectomy, this level was significantly higher than that of 70% hepatectomy. Total ketone body concentrations in arterial blood of 25% hepatectomized rabbits

Table 2. NEFA, ketone body ratio and total ketone body concentrations in arterial blood at 12 hours after 25 and 70% hepatectomy.

Operation	NEFA (mEq/L)	AcAc BOHB	AcAc+BOHB (μmoles/ml)
Control (overnight fasting)	0.430±0.025 (29)	0.904±0.092 (20)	0.086±0.007 (20)
25% Hepatectomy	0.486±0.038 (9)	0.620±0.024 (8)	0.259±0.041 (9)
70% Hepatectomy	0.980±0.110*(11)	0.415±0.025*(30)	0.210±0.014 (32)

Values given are means±SEM. Numbers in parentheses indicate number of animals.
NEFA=non-esterified fatty acid. AcAc=acetoacetate. BOHB=β-hydroxybutyrate.
*= $p < 0.001$ compared with 25% hepatectomized rabbits.

Table 3. Effects of portal infusion of (+)-octanoylcarnitine on hepatic adenine nucleotides at 12 hours after 25 and 70% hepatectomy.

Treatment	(n)	Adenine Nucleotides (μ moles/gr wet liver)				Energy Charge
		ATP	ADP	AMP	Total	
Normal	(11)	2.88 ± 0.10	0.55 ± 0.03	0.13 ± 0.01	3.57 ± 0.10	0.885 ± 0.006
Sham Operation	(4)	2.06 ± 0.04	0.60 ± 0.06	0.15 ± 0.09	2.81 ± 0.10	0.840 ± 0.014
25% Hepatectomy	(6)	2.44 ± 0.13	0.74 ± 0.09	0.21 ± 0.03	3.38 ± 0.21	0.830 ± 0.013
+Saline P.I.	(4)	1.99 ± 0.18	1.02 ± 0.10	0.35 ± 0.05	3.36 ± 0.07	0.744 ± 0.031
+O.C. P.I.	(4)	1.82 ± 0.24	1.14 ± 0.11	0.32 ± 0.04	3.28 ± 0.14	0.726 ± 0.031
70% Hepatectomy	(4)	1.75 ± 0.07^a	0.78 ± 0.09	0.20 ± 0.03	2.73 ± 0.16^c	0.782 ± 0.015^c
+Saline P.I.	(5)	1.46 ± 0.02	0.83 ± 0.08	0.35 ± 0.04	2.64 ± 0.10^a	0.701 ± 0.010
+O.C. P.I.	(7)	0.81 ± 0.10^a	1.01 ± 0.05	0.77 ± 0.13^c	2.59 ± 0.10^b	0.510 ± 0.039^b

Values given are means \pm SEM. Numbers in parentheses indicate number of animals. Total = total adenine nucleotides. P.I. = portal infusion. O.C. = (+)-octanoylcarnitine.

a = $p < 0.001$, b = $p < 0.01$, c = $p < 0.05$ compared with the similarly treated rabbits in 25% hepatectomy.

were slightly higher than those of 70% hepatectomized rabbits at 12 hours after the operation.

Table 3 shows the comparison of the effects of portal infusion of (+)-octanoylcarnitine on hepatic adenine nucleotides between 25 and 70% hepatectomized rabbits at 12 hours after the operation. In 25% hepatectomy, energy charge level did not decrease compared with those for normal and sham operated rabbits. Portal infusion of (+)-octanoylcarnitine did not decrease the energy charge level significantly, beyond that for saline infusion. In contrast, in 70% hepatectomy, the energy charge level decreased significantly, compared with those for normal and sham operated rabbits ($p < 0.05$). Portal infusion of (+)-octanoylcarnitine further decreased the energy charge level remarkably, beyond that for saline infusion ($p < 0.01$).

The next experiment was performed to confirm the fact that the predominant oxidation of fatty acids by the remnant liver after major hepatectomy was not the result of the exhaustion of blood glucose and liver glycogen. In this experiment, an intravenous administration of a 20% glucose solution was continued for 15 hours after the operation to maintain the blood sugar level

Table 4. Effects of postoperative intravenous glucose administration on blood sugar level, NEFA level, blood ketone body ratio and total ketone body concentrations in arterial blood at 12 hours after 70% hepatectomy.

Treatment	Blood sugar (mg/dl)	NEFA (mEq/L)	AcAc/BOHB	AcAc+BOHB (μ moles/ml)
Control	130 ± 5 (16)	0.430 ± 0.025 (29)	0.904 ± 0.092 (20)	0.086 ± 0.007 (20)
70% Hepatectomy	109 ± 4^a (16)	0.980 ± 0.110^a (11)	0.415 ± 0.025^a (30)	0.210 ± 0.014^a (32)
70% H.+Glucose	235 ± 13^b (7)	0.404 ± 0.014^b (7)	0.533 ± 0.080^n (7)	0.070 ± 0.002^b (7)

Values given are means \pm SEM. Numbers in parentheses indicate number of animals. 70% H.+Glucose = rabbits received intravenous administration of a 20% glucose solution immediately after 70% hepatectomy. NEFA = non-esterified fatty acid. AcAc = acetoacetate. BOHB = β -hydroxybutyrate.

a = $p < 0.001$ compared with the control group. b = $p < 0.001$ compared with 70% hepatectomy only. n = not significant ($0.05 < p < 0.10$) compared with 70% hepatectomy only.

Table 5. Effects of portal infusion of (+)-octanoylcarnitine on hepatic adenine nucleotides during the intravenous administration of a 20% glucose solution after 70% hepatectomy.

Portal Infusion	(n)	Adenine Nucleotides (μ moles/gr wet liver)				Energy Charge
		ATP	ADP	A.M.P	Total	
Saline	(3)	1.52 \pm 0.16	0.72 \pm 0.13	0.39 \pm 0.08	2.63 \pm 0.05	0.716 \pm 0.049
(+)-O.C.	(4)	0.62 \pm 0.19 ^a	0.55 \pm 0.06	0.53 \pm 0.13	1.70 \pm 0.18 ^a	0.518 \pm 0.077 ^b

Values given are means \pm SEM. Numbers in parentheses indicate number of animals. (O.C.=octanoylcarnitine. Total=total adenine nucleotides. a= $p<0.01$, b= $p<0.05$ compared with intraportally saline infused rabbits.

Intravenous administration of a 20% glucose solution was continued for 15 hours after operation to maintain the blood sugar level above 200 mg/dl. (+)-Octanoylcarnitine (5 μ moles) was infused intraportally for 3 hours from 12 hours after the operation. As a control, saline was infused intraportally instead of (+)-octanoylcarnitine solution.

above 200 mg/dl. (+)-Octanoylcarnitine was infused intraportally from 12 hours to 15 hours after 70% hepatectomy. The effects of postoperative intravenous administration of glucose solution on NEFA level, blood ketone body ratio and total ketone body concentrations in arterial blood after 70% hepatectomy are shown in Table 4. Although NEFA level and total ketone body concentrations in arterial blood did not increase by postoperative intravenous glucose administration, blood ketone body ratio still remained at a low level. The effects of portal infusion of (+)-octanoylcarnitine on hepatic adenine nucleotides and energy charge level during intravenous glucose administration are shown in Table 5. Despite hyperglycemia, portal infusion of (+)-octanoylcarnitine markedly decreased the energy charge level to 0.518 compared with 0.716 for intraportally saline infused rabbits at this stage ($0.01<p<0.05$).

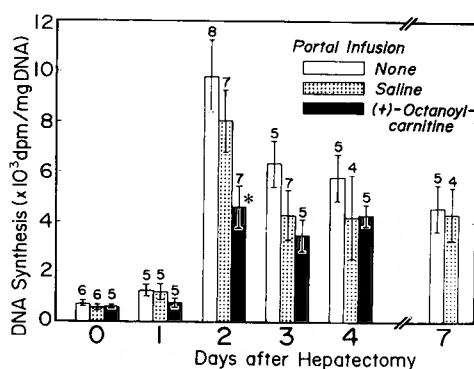


Fig. 6. Time course of the rate of (methyl-³H)thymidine incorporation into DNA of the regenerating liver after 70% hepatectomy of rabbits, and the effects of portal infusion of (+)-octanoylcarnitine on the rate of DNA labelling. Open bars indicate the time course of the rate of DNA synthesis after 70% hepatectomy. Stippled bars indicate the values for control rabbits which received an intraportal saline infusion. Solid bars indicate the values for rabbits which received an intraportal (+)-octanoylcarnitine infusion. Numbers above the bars are the numbers of rabbits in each group and vertical lines indicate standard errors. * = Significantly decreased from saline-infused rabbits ($p<0.05$). There was no statistically significant difference in DNA synthesis between the saline-infused and non-infused rabbits on any postoperative days.

Fig. 6 shows the time course of the rate of (methyl- ^3H) thymidine incorporation into DNA of the regenerating liver after 70% hepatectomy of rabbits, and the effects of portal infusion of (+)-octanoylcarnitine on the rate of DNA labelling. At 24 hours after 70% hepatectomy, the rate of DNA labelling in the regenerating liver had risen only to 1.7 times the non-hepatectomized normal value. At 48 hours, however, the rate of DNA labelling had increased abruptly, up to 13.8 times the normal value, with a subsequent decrease to 6.5 times the normal value on the seventh postoperative day. Intraportal infusion of (+)-octanoylcarnitine resulted in a decrease in the rate of DNA labelling from 14.4 times to 8.2 times the control (non-hepatectomized, but infused intraportally with saline) value at 48 hours after hepatectomy ($p < 0.05$). However, the (+)-octanoylcarnitine infusion did not have a significant effect on the rate of DNA labelling at 72 hours or later after 70% hepatectomy.

Discussion

The energy charge level, which indicates a metabolically available energy pool, is normally maintained at a constant level. In this dynamic steady state, a rise in energy expenditure in the cells would result in a decrease of the energy charge, unless this is accompanied by a concomitant increase in the rate of mitochondrial phosphorylation of ADP to ATP. The energy charge level of the cell is important as an index of such cellular energy status for understanding the range of equilibrium between energy-generating and energy-utilizing reactions within hepatic cells.

At 12–24 hours after 70% hepatectomy, energy charge level of the remnant liver decreased rapidly because of the enormous energy demand, for example, to clear hepatodepressant factors, such as portal vein ammonia, from the blood stream³⁷.

This period appears to be the time when the metabolic overload is maximally imposed upon the remnant liver and the delicate energy balance in the remnant liver is barely maintained by a compensatory enhancement of mitochondrial phosphorylative activity. The mortality rate of hepatectomized rabbits was high during this period.

Serum NEFA level increased rapidly to its maximum at 12 hours after 70% hepatectomy, with a concomitant rise in blood total ketone body concentrations. The elevated NEFA level indicate the enhanced mobilization of fatty acids from the adipose tissue rather than decreased utilization considering from their short half life times²⁹.

Considering from the facts that most of the fatty acids oxidized go to water soluble products other than ketone bodies, that the liver is the only organ that makes a net contribution of ketone bodies to the blood stream⁴⁵, and that the mass of the remnant liver is a part of the whole liver, the elevated total ketone body concentrations in the arterial blood indicates highly enhanced ketogenesis in the remnant hepatic tissue. Although total ketone body concentrations in arterial blood after 70% hepatectomy were not higher than those in 25% hepatectomized rabbits at 12 hours after hepatectomy, considering that the mass of the remnant liver is only 30% of the normal liver, the enhancement of ketogenesis per unit of remnant liver is greater in 70% hepatectomized rabbits than in 25% hepatectomized rabbits⁴⁴.

The ratio of ketone bodies in the liver is in equilibrium with the free NAD^+/NADH ratio

in the mitochondria⁴⁶⁾. In liver mitochondria, acetoacetate undergoes reduction to β -hydroxybutyrate by β -hydroxybutyrate dehydrogenase. Since this enzyme exclusively localizes in the liver mitochondria, and since acetoacetate and β -hydroxybutyrate freely permeable the hepatocyte to the circulation, the ratio of acetoacetate to β -hydroxybutyrate in arterial blood can be said indicative of the mitochondrial free NAD^+/NADH ratio⁴²⁾. Moreover, the free NAD^+/NADH ratio in the mitochondria decreases in the oxidation of free fatty acids⁴⁴⁾. Thus, a marked decrease in the blood ketone body ratio at 12 hours after 70% hepatectomy would also indicate an enhanced oxidation of free fatty acids in the light of high NEFA level and high total ketone body concentrations in the blood.

In addition, the portal infusion of a potent inhibitor of fatty acid oxidation, (+)-octanoylcarnitine, markedly decreased the energy charge at 12–24 hours after 70% hepatectomy. In the course of fatty acid oxidation, fatty acids are activated to fatty acyl-CoA by fatty acyl-CoA synthetase in the cytosol. To cross the mitochondrial inner membrane, fatty acyl-CoA must be transformed to fatty acyl carnitine by the action of carnitine acyltransferase. In the mitochondrial matrix, fatty acyl carnitine is transformed again to fatty acyl-CoA by a second type of carnitine acyl-transferase. Fatty acyl-CoA which is so formed receives subsequent oxidation in the mitochondrial matrix⁷⁾. Octanoyl esters of (+)-carnitine block the β -oxidation of fatty acids by inhibiting the action of carnitine acyltransferase^{20,21,22,32,48)}. Therefore, these results indicate that enhanced fatty acid oxidation is the main energy source of the remnant liver at 12–24 hours after major hepatectomy. However, at later infusion, with the restoration of the energy charge, (+)-octanoylcarnitine had less effect and became insignificant at 96 hours after the operation. In contrast, the intraportal infusion of an inhibitor of glycolysis, sodium fluoride, did not affect the energy charge at 12–24 hours after hepatectomy. Afterwards, the infusion of sodium fluoride decreased the energy charge level and enhanced the ketogenesis at 48–96 hours after major hepatectomy. These results mean that when the energy charge level of the remnant liver decreases markedly, the ATP synthesis of the liver mitochondria is mainly dependent upon the fatty acid oxidation, and thereafter mainly dependent upon glucose oxidation in the course of the restoration of energy charge level. It seems likely that the energy supply derived from β -oxidation of fatty acids, rather than glucose oxidation, is more effective in restoring the energy charge level of the remnant liver. These results seem to be consistent with the report of NEELY et al.²⁸⁾, that in hearts perfused by glucose solution alone, the citric acid cycle was generally “run down” and the phosphate potential was low, while in those perfused with fatty acids, the phosphate potential was maintained at high levels. The fact that the fatty acid oxidation system is easily reactivated by the administration of sodium fluoride at 48–96 hours after major hepatectomy supports the likelihood of prior enhancement of fatty acid oxidation.

In 25% hepatectomized rabbits, the energy charge level of the remnant liver remained unchanged after the operation, and was not affected by the portal infusion of (+)-octanoylcarnitine. After 25% hepatectomy, even in the early postoperative period, ATP synthesis of the remnant liver mitochondria is mainly dependent upon glucose oxidation. It seems likely that the energy status of the remnant liver cells determines which substrate, glucose or fatty acids,

is predominantly oxidized to synthesize ATP. In the critical period of decreased energy charge level, mitochondrial redox state undergoes reduction which is favorable for the oxidation of fatty acids.

In 93% hepatectomized rabbits, compensatory mitochondrial hyperfunction could not occur because of the enormous degree of metabolic derangement. The remnant liver mitochondria could not oxidize glucose or fatty acids as substrates in adequate quantity. The rapid decrease of blood ketone body ratio reflects the extinction of the mitochondrial function.

Impaired glucose tolerance simultaneously developed with a decrease in the energy charge level of the remnant liver after major hepatectomy. In view of the key position of the liver in maintaining glucose homeostasis, it is not surprising that hepatectomy leads to some alteration in carbohydrate metabolism. The energy charge level decreased significantly after portal infusion of (+)-octanoylcarnitine even during the intravenous administration of a glucose solution in 70% hepatectomized rabbits. This fact reveals that the remnant liver cannot utilize blood glucose as an energy source despite hyperglycemia in the critical period after major hepatectomy. Hence, the exhaustion of liver glycogen is not the key factor for enhanced fatty acid oxidation. This study suggests that the influence of intracellular fatty acid metabolism, rather than that of extracellular concentrations of free fatty acids, is more important factor in glucose metabolism.

The degree of impairment in glucose tolerance is closely correlated with the decrease in blood ketone body ratio, which in turn indicates an enhanced fatty acid oxidation. The β -oxidation of fatty acids results in the production of reducing equivalents (NADH) and acetyl-CoA. It has been found that the oxidation of fatty acids may inactivate and inhibit the pyruvate dehydrogenase complex by elevating the mitochondrial ratio of NADH/NAD⁺ and acetyl-CoA/CoASH, and that the ratio of ATP/ADP is not the sole regulatory parameter for pyruvate dehydrogenase complex activity. Thus, NADH/NAD⁺ ratios are of primary importance in the inhibition of oxidation of pyruvate formed from glucose²⁾. The measurement of blood ketone body ratios should gain wide acceptance as a standard method for classifying the changes in the energy status of the remnant liver after hepatic resection⁴⁴⁾.

In the present study, the effect of fatty acid oxidation on the rate of DNA synthesis in the regenerating liver after major hepatectomy has studied. The phenomenon of apparent dormancy in the rate of (methyl-³H)thymidine incorporation into the DNA in the initial stage of regeneration has been reported by other investigators in studies with partially hepatectomized rats³⁾. Such a delay in the regeneration process early after partial hepatectomy has also been reported by several investigators in morphological or chemical studies on rats⁸⁾, dogs⁶⁾, and pigs¹³⁾. In rats, and probably in rabbits, dogs and pigs as well, this may be accounted for by the time required to induce and/or increase the activities of enzymes involved in DNA synthesis, such as ribonucleic acid polymerase^{5,43)} and thymidine kinase⁹⁾. The metabolic responses to partial hepatectomy differ according to the species of animals, and in rats peak DNA synthesis in hepatocytes occurred at 20–24 hours after partial hepatectomy³⁾, whereas in rabbits it occurred at 48 hours.

In partially hepatectomized rats in which about 68% of the hepatic tissue had been excised, the energy charge level of the remnant liver decreased only slightly and temporarily⁴⁹⁾ whereas

in similarly hepatectomized rabbits, a marked and rapid decrease in the energy charge level occurred¹⁴⁾. Therefore the delay in the onset of DNA synthesis in rabbits may reflect the decreased energy charge level of the remnant liver, which would have an adverse effect on DNA synthesis. Considering the fact that the energy charge level of the remnant liver returned to 0.793 at 48 hours after 70% hepatectomy of rabbits¹⁴⁾, it seems likely that the restoration of the energy charge level of the remnant liver to 0.8 or more is necessary for marked enhancement of DNA synthesis to occur.³⁶⁾

Although the remnant liver is able to utilize glucose to a considerable degree at 48 hours after 70% hepatectomy in rabbits^{24,25)}, the fact that portal infusion of (+)-octanoylcarnitine significantly decreased the rate of DNA labelling reveals that fatty acid oxidation is still an important energy source for DNA synthesis at this time. As (+)-octanoylcarnitine did not affect the rate of DNA labelling at 72 hours, it may be concluded that the remnant liver from that point on was able to acquire a sufficient ATP supply for DNA synthesis by glycolysis.

This study revealed that the remnant liver cannot utilize glucose as a substrate, and, conversely, fatty acids are preferentially oxidized as a substrate which provides an ATP supply in the phase immediately following major hepatic resection²⁶⁾. Postoperative intravenous administration of a 20% glucose solution decreased blood NEFA level and ketogenesis. Mobilization of free fatty acids from peripheral adipose tissue was suppressed probably due to the increase in blood sugar level. Therefore, the standard postoperative administration of hyperosmolar glucose solution and insulin should be carefully reconsidered, because of the resultant decrease in free fatty acids mobilization which are the only substrate that can be oxidized in the phase immediately following major hepatic resection. SIMEK et al.⁴¹⁾ also reported the inadvisability of postoperative glucose administration after partial hepatectomy of rats.

OCHSNER et al.³¹⁾ and McDERMOTT and WEBER¹⁹⁾ reported an immediate decrease in blood sugar levels in patients after major hepatectomy, and McDERMOTT and OTTINGER¹⁸⁾ reported that hypoglycemia is a serious and sometimes lethal problem after extensive removal of liver tissue in experimental animals. The authors of these reports^{18,19,31)} recommended constant intravenous administration of a 10% glucose solution; PINKERTON et al.³⁸⁾ even recommended that total parenteral nutrition should be administered in the immediate postoperative period and continued until the patient can resume adequate oral nutrition. Judging from the results of the present study, however, it is very important that glucose administration is maintained at a level which does not inhibit the mobilization of fatty acids from adipose tissue to the remnant liver during the early postoperative period following major hepatectomy. For this purpose the administration of a 5% glucose solution should be considered sufficient. Insulin administration in the phase immediately following major hepatectomy should be reconsidered, because it also inhibits the mobilization of fatty acids from adipose tissue to the remnant liver. The problems of what substrates to administer during the critical stages after major hepatectomy remain for further investigation. Enemas with antibiotics or lactulose have been shown in animal experiments to restore decreased energy stores in the remnant liver after partial hepatectomy^{30,50)}, and may have a beneficial effect on hepatic regeneration clinically.

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和文抄録

肝切除後のエネルギー基質の変化 ——大量肝切除後における脂肪酸の優先的 利用と、その肝再生に及ぼす影響——

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25, 70及び93%肝切除家兎において、残存肝のエネルギー状態の違いに対応して、残存肝で利用され得るエネルギー基質にどのような差異が生じるかを検討した。25%肝切除家兎においては術後も残存肝のエネルギーチャージ ($(\text{ATP} + 0.5\text{ADP})/(\text{ATP} + \text{ADP} + \text{AMP})$) は低下せず、かつ、脂肪酸酸化阻害剤である(+)オクタノイルカルニチンの門脈内投与によっても影響を受けなかった。従って25%肝切除後に残存肝で利用されるエネルギー基質は主としてグルコースであり、脂肪酸酸化に頼ってはいなかった。しかし一方、70%肝切除後には残存肝のエネルギーチャージは急速に低下し、術後に12-24時間には0.77の最低値に達した ($p < 0.01$)。この時点で(+)オクタノイルカルニチンを投与すると、エネルギーチャージは更に0.51にまで低下した。70%肝切除後96時間目にはエネルギーチャージはほぼ正常値に近くまで回復した。このようにエネルギーチャージが回復した時点では(+)オクタノイルカルニチンは

エネルギーチャージに影響を与えなかったが、むしろ解糖阻害剤であるフッ化ナトリウムによりエネルギーチャージが低下する傾向がみられた。フッ化ナトリウムは70%肝切除後12-24時間には影響しなかった。93%肝切除後には残存肝のエネルギーチャージは術直後より急激に低下した。以上の事実より、残存肝における代謝は、そのエネルギーチャージが低下している時にはエネルギー源として主に脂肪酸を酸化し、エネルギーチャージが回復してくるにつれてグルコースを利用できるように転換してゆくものと考えられた。また脂肪酸酸化は残存肝のエネルギーチャージを維持し、上昇させる事によってエネルギー的に肝再生の亢進に寄与していると考えられた。広汎肝切除後の早期に高張糖液やインスリンを投与する事は、これらが脂肪組織からの脂肪酸の動員を抑制する事から、再検討すべきである点についても言及した。